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Formulation and Evaluation of Diclofenac Sodium-Loaded Solid Lipid Nanoparticles in Ceramide Cream for the Treatment of Atopic Dermatitis

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Formulation, Evaluation of Diclofenac Sodium,

ABSTRACT:

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by impaired skin barrier function and recurrent episodes of itching and inflammation.

Conventional therapies often involve corticosteroids, which, although effective, pose long-term side effects such as skin thinning and immunosuppression. This study aimed to develop a novel, non-steroidal topical formulation by incorporating Diclofenac Sodium (DS), a non-steroidal anti-inflammatory drug (NSAID), into

Solid Lipid Nanoparticles (SLNs) and embedding them in a ceramide- based cream to address both inflammation and barrier dysfunction in AD.

DS-loaded SLNs were prepared using high-shear homogenization followed by ultrasonication, employing glyceryl monostearate as the lipid and Tween 80 as the surfactant. The optimized formulation demonstrated a nanoscale particle size (150–180 nm), low polydispersity index (PDI < 0.3), and high zeta potential (> −30 mV), indicating good stability. These SLNs were then incorporated into a ceramide-rich oil-in-water cream base, formulated to enhance skin Epidermal barrier commonly seen in AD patients.

Physicochemical evaluations revealed that the final formulation had a skin-friendly pH (~5.6), suitable viscosity, excellent spreadability, and no signs of phase separation or aggregation. The formulation demonstrated sustained release behavior of DS in in vitro studies, suggesting prolonged anti-inflammatory action at the site of application.

The combined approach of barrier restoration via ceramides and targeted drug delivery via SLNs presents a promising therapeutic alternative to corticosteroids for AD management. This study supports the potential of DS-loaded SLNs in ceramide cream as a safe, effective, and patient-compliant strategy for treating chronic inflammatory skin conditions.

1. Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease marked by xerosis, erythema, itching, and eczematous lesions, commonly beginning in childhood but persisting or appearing in adulthood [1]. Globally, AD has become a major dermatological concern, with the highest prevalence in children aged 0–5 Years (16.0%) and an overall prevalence of 11.1% in children and adolescents and 6.3% in adults [2]. In 2021, 10.2 million pediatric cases were reported worldwide, a 4.8% increase since 1990, and the disease burden in disability-adjusted life years (DALYs) is expected to rise with aging and population growth [3].

The pathophysiology of AD involves epidermal barrier dysfunction, genetic factors, and immune

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dysregulation, and environmental triggers. Mutations in the filaggrin (FLG) gene reduce natural moisturizing factor (NMF) production, leading to impaired hydration and skin barrier integrity [4–5]. Along with filaggrin deficiency, reduced ceramide levels in the stratum corneum compromise lipid organization, increase transepidermal water loss (TEWL), and predispose the skin to allergen penetration and microbial colonization [6–7]. This barrier disruption initiates immune activation, creating a cycle of inflammation and barrier deterioration [8].

Filaggrin mutations are found in 10–50% of AD patients and are strongly linked to early-onset and severe disease [10–11]. Ceramide deficiency further weakens the barrier [7, 9, 12–13]. Immune imbalance plays a central role, with acute AD characterized by Th2-dominant cytokines (IL-4, IL-13, and IL-31) and chronic AD showing Th1 and Th22 responses [14–19]. Elevated IgE levels, mast cell activation,

2. Materials and Methods

2.1 Materials:

The materials were procured from reliable suppliers to ensure quality and consistency. Diclofenac sodium was purchased from Mumbai, while glyceryl monostearate, Tween 80, lecithin, ceramide, stearic acid, carbopol, and phosphate buffer saline And cytokine-induced suppression of barrier proteins aggravate the condition [20]. Conventional therapies, including emollients, corticosteroids, calcineurin inhibitors, and systemic immunosuppressants, provide symptomatic relief but are limited by adverse effects, relapses, and safety concerns [22–25]. Diclofenac sodium (DS), a non-steroidal anti-inflammatory drug, shows promise as a safer alternative with strong anti- inflammatory effects and fewer risks such as skin atrophy or immunosuppression. However, its poor solubility and limited penetration reduce topical efficacy [26–29]. Advanced delivery systems such as solid lipid nanoparticles (SLNs) enhance DS penetration, provide sustained release, and protect against degradation, making them suitable for long-term AD management [30–33]. In parallel, ceramide-based formulations address lipid deficiencies, restore barrier function, reduce TEWL, and improve hydration. Clinical studies indicate that ceramide creams outperform standard moisturizers and reduce corticosteroid dependence [34–36].

Thus, combining SLN-based DS delivery with ceramide-containing formulations offers a dual therapeutic strategy that simultaneously targets inflammation and barrier dysfunction, providing a safer and more effective approach for atopic dermatiis management.

(pH 7.4) were obtained from CDH, Delhi (India). Distilled water was prepared in-house.

2.2 Preformulation Studies Preformulation studies were conducted to evaluate the physicochemical properties of Diclofenac Sodium and its suitability for formulation development. The drug was first examined visually to record its Physical appearance. Its melting point was determined using the capillary method with a melting point apparatus, and the experiment was repeated thrice to obtain an average value. Solubility profiling was performed in different solvents by dissolving the drug in measured volumes, followed by filtration and analysis using UV spectroscopy to establish equilibrium solubility. For identification,

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chemical tests were carried out: the Ferric Chloride test, which produced a violet coloration confirming the phenylacetic acid structure, and the Sodium Hydroxide with heat test, which yielded a yellow to orange coloration indicating the presence of an aromatic amino group. These preliminary evaluations ensure the drug's identity, stability, and compatibility before proceeding to formulation design.

2.3 Spectroscopic Studies

Spectroscopic analysis of Diclofenac Sodium was performed to confirm its identity and structural characteristics. The UV spectrum in methanol was recorded between 200–400 nm to determine the drug's absorbance profile, while IR spectroscopy using the KBr disc method provided information on functional groups and molecular structure.

2.4 Analytical Method Development

Phosphate buffer saline (PBS, pH 7.4) was prepared to maintain physiological conditions for analysis. A calibration curve of Diclofenac Sodium was constructed in methanol over a range of 2–20 µg/mL to enable accurate quantification in subsequent experiments.

2.5 Incorporation of DS-SLNs into Ceramide-Based Cream

Table: 1 Preparation of Cream Base Preparation

Ingredient	Purpose	Example(s)
Emulsifying Wax	Stabilizes the oil-water emulsion	Polysorbate 80
Ceramides	Repair the skin barrier and enhance hydration	Ceramide2, Ceramide 3
Humectants	Attracts water to the skin	Glycerin
Preservatives	Prevents microbial contamination	Phenoxyethanol,
Water	Serves as the aqueous phase	Distilled water

2.6 Procedure for Cream Base Preparation:

Heat Oil Phase: Emulsifying wax and ceramides were melted at 70–75°C until homogeneous form was obtained.

Heat Aqueous Phase: Then water was heated and dissolved in glycerin and other water-soluble components at 70–75°C.

Combine Phases: Then aqueous phase was mixed in the oil phase with continuous stirring and then homogenized till a stable emulsion was obtained. (32).

Incorporation of DS-SLNs into Cream Base

Prepare DS-SLN Dispersion: After

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Confirming optimized SLNs with suitable size, zeta potential, and drug loading.

Cool Cream Base: Ensure the base is cooled below 40°C to preserve SLN integrity beforehand only.

Add DS-SLN Dispersion: Then gradually SLN dispersion to the cooled cream base with gentle stirring will be done.

Mixing: Then magnetic stirring or gentle homogenization will be used for uniform distribution.

2.7 Optimization of diclofenac sodium loaded solid lipid nanoaprticles using central composite design

Various factors that may affect the quality of diclofenac sodium loaded solid lipid nanoparticles were investigated, which consisted of the amount of lipid, surfactants, and drug. The encapsulation of a drug is significantly affected by the lipid which is an important component of SLNs. The development of diclofenac sodium- loaded solid lipid nanoparticles and the evaluation of the impact of two formulation parameters (amount of stearic acid and amount of tween 80) on formulation characteristics were carried out using a central composite experimental design. Using 3D surface plots, the impact of these two variables on the percentage entrapment efficiency (EE %) was investigated.

2.8 Physicochemical Evaluation of the Formulated Cream

The pH of topical creams is a critical parameter to ensure skin compatibility, particularly in diseased conditions such as atopic dermatitis. The formulation was dispersed in distilled water, and the pH was measured using a calibrated digital pH meter, with values maintained within the acceptable range of 5.0–6.5 for Dermal use. Viscosity plays an important role in determining spreadability and patient acceptance; hence, it was measured using a Brookfield Viscometer at controlled temperature (25 ± 1 °C), with results expressed in centipoise. Spreadability, which reflects the ease of application, was evaluated by the slip and drag method, where the cream's ability to spread under a defined weight was quantified, with higher values indicating better usability. Zeta potential, a measure of electrostatic stability of solid lipid nanoparticles, was analyzed using a Zetasizer, where values beyond ±30 mV indicated sufficient repulsion to prevent particle aggregation and ensure dispersion stability.

2.9 In vitro release studies

In vitro drug release studies was carried out using a dialysis bag method. the is placed in the donor compartment, and a suitable receptor medium (such as phosphate-buffered saline, pH 7.4) is used in the receptor compartment. The system is maintained at 32–37°C to simulate skin temperature and stirred continuously.

At predetermined time intervals (e.g., 0.5, 1, 2, 4, 6, 8, 12, and 24 hours),

Small samples are withdrawn from the receptor compartment and replaced with fresh medium to maintain sink conditions.

2.10 Preparation of Solid Lipid Nanoparticles (SLNs)

Diclofenac Sodium Solid Lipid Nanoparticles (SLNs) were prepared by the emulsification–sonication method using stearic acid and soya lecithin as the lipid phase, and Poloxamer 188

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with Tween 80 as stabilizers in the aqueous phase. The drug-loaded aqueous solution was mixed with the molten lipid, homogenized, and sonicated to obtain a fine nanodispersion, followed by rapid cooling to solidify the lipid matrix. Different batches (DDSLN1–DDSLN13) were optimized for particle size and entrapment efficiency, with the best formulation (DDSLN14) showing ~200 nm size and maximum drug entrapment.

2.11 In-Vitro Characterization of Diclofenac-Sodium–Loaded Solid Lipid Nanoparticles and Their Creams

1. Physical Appearance – Checked for colour, homogeneity, phase separation, and sedimentation after 24 h at 25 °C.

2. **Percentage Drug Entrapment (EE %)** – Free drug separated by ultracentrifugation; supernatant analysed by UV–Vis spectrophotometry at 276 nm.

3. Particle Size, PDI & Zeta Potential – Measured by dynamic light scattering and electrophoretic light scattering using Malvern Zetasizer.

4. Transmission Electron Microscopy (TEM) – Morphology observed by TEM after negative staining with phosphotungstic acid.

2.12 Formulation of SLN-Loaded Creams

Cream base – Stearic acid (10 % w/w), cetyl alcohol (3 %), mineral oil (5 %), glycerol (5 %), triethanolamine (q.s. to pH 6.0) and purified water (up to 100 %).

Incorporation – SLN dispersion (equivalent to 1 % diclofenac sodium) replaced an equal weight of water and was blended into the cooled (<40 °C) base with gentle stirring. Four lipid-concentration levels produced DDSLN14C1–C4.

2.13 Cream Characterisation

The cream formulations were evaluated for appearance by visual inspection after 24 h and freeze–thaw cycles, while pH was measured by dispersing cream in distilled water and using a digital pH meter at 25 °C. Spreadability was assessed by the slip and drag method with glass plates, and viscosity was determined using a Brookfield viscometer (spindle #64, 50 rpm, 25 °C). Drug content was quantified by dissolving cream in ethanol–PBS (1:1), followed by filtration and UV spectrophotometric analysis at 276 nm.

2.14 In-Vitro Drug Release

Diffusion set-up – Franz diffusion cells (effective area = 2.54 cm², receptor = 25 mL) with cellulose acetate membrane (MWCO 12 000 Da) pre-soaked in PBS pH 7.4.

Donor – 1 g cream (containing ~10 mg diclofenac sodium).

Receptor medium – PBS pH 7.4 + 20 % ethanol, maintained at 32 ± 0.5 °C, stirred 600 rpm.

Sampling – 1 mL withdrawn at predetermined times (0–24 h) and replaced with fresh medium. Samples filtered (0.45 µm) and analysed spectrophotometrically. Sink conditions (C < 10 % Csat) were verified.

Control – Drug-loaded conventional o/w cream prepared identically but without SLNs.

2.15 Release-Kinetic Modelling Cumulative % drug release vs. time data (mean ± SD) were fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas models using Microsoft Excel Solver. Regression

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Coefficients (R^2) were compared; the highest R^2 indicated the best-fit mechanism.

2.16 Statistical Analysis

All quantitative results were analysed in OriginPro 2024. Normality was confirmed (Shapiro–Wilk). One-way ANOVA followed by Tukey's post-hoc test assessed inter-formulation difference.

($\alpha = 0.05$).

3. Results:

3.1 Preformulation Studies

1. Appearance of Drug

Graphs (Figures 7.7–7.9, etc.) display mean ± SD with n = 3.

The physical characteristics of Diclofenac Sodium were evaluated visually. All parameters were found within the acceptable limits as reported in official monographs.

Table 2: Appearance Properties of Diclofenac Sodium

Properties	Observation
Color	White to off-white crystalline
Odor	Odorless
Nature	Crystalline Powder
Taste	Slightly Bitter

2. Solubility Profile

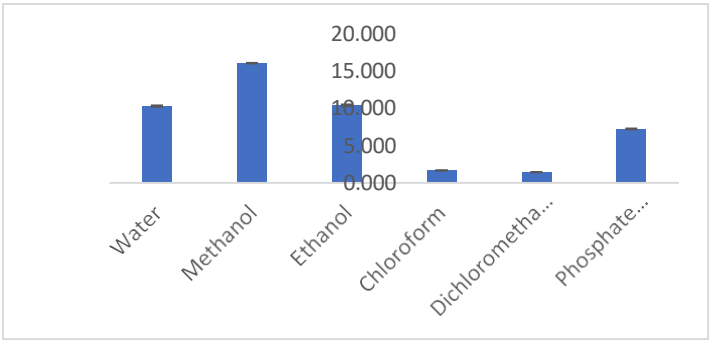

Figure 1: Solubility of diclofenac sodium in various water soluble, water miscible solvent and non-organic solvent

3. Melting Point

The melting point of Diclofenac Sodium was found to be in the range of 283-285°C.

This matches the official pharmacopeial values and confirms the purity of the drug substance.

3.2 Spectroscopic Studies

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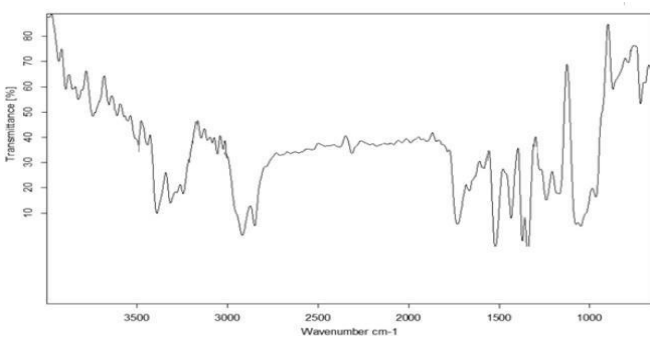

Fig 2 FTIR of Diclofenac sodium

3.3 Analytical Method Development

a) Calibration Curve of Diclofenac Sodium (in Methanol)

The linear graph yielded the regression

Equations y = 0.034x + 0.0125 with regression coefficient R^2 of 0.999, indicating good linearity

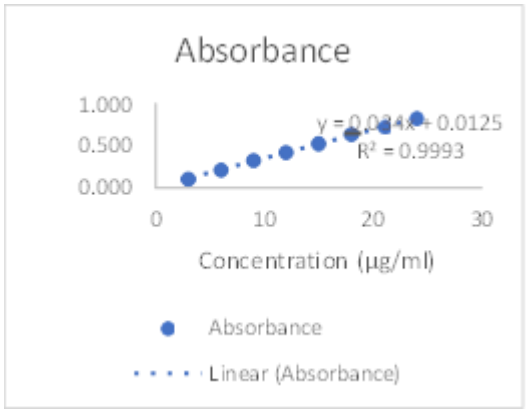

Fig 3 Caliberation Curve

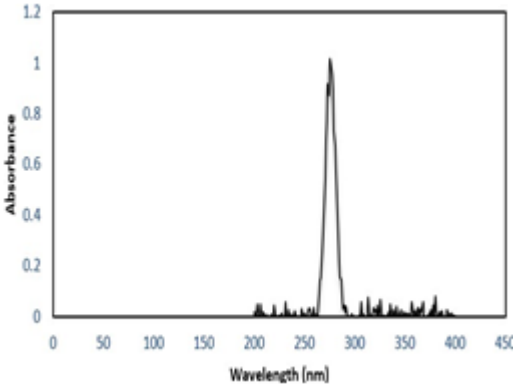

Fig 4 UV spectra

3.4 Preparation of Diclofenac Sodium-Loaded Solid Lipid Nanoparticles

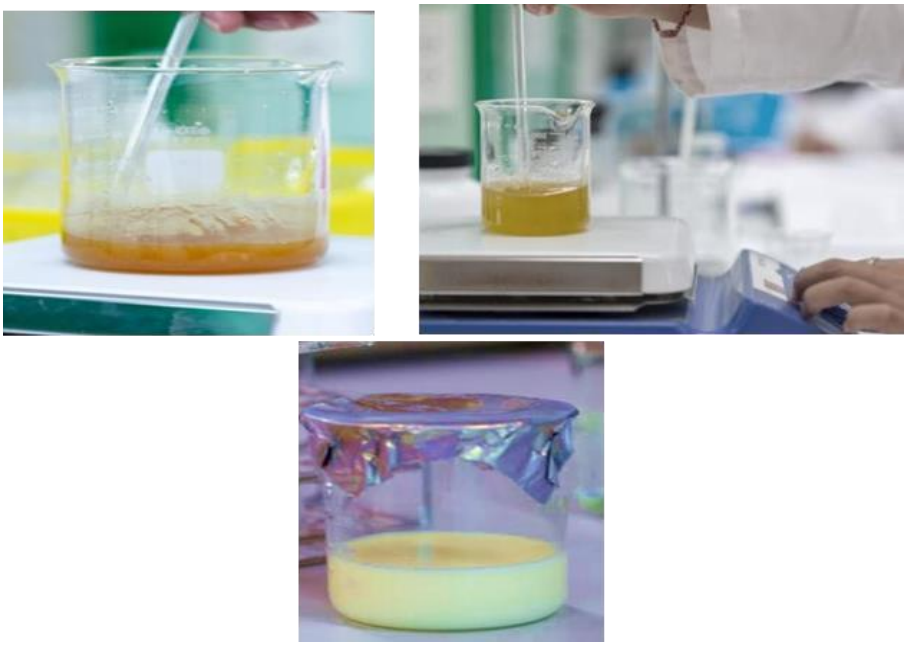

Fig 5: (a) the oily phase, (b) the aqueous phase, (c) the final emulsion

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3.5 Optimization of Diclofenac Sodium Loaded Solid Lipid Nanoaprticles Using Central Composite Design

Thirteen runs totaling different numbers of independent formulation parameters were developed. Next, the EE% of each prepared formulation was examined. The vOptimization goal was set to obtain a formulation with maximum entrapment efficiency percentage. The characteristics of different solid lipid nanoaprticles formulations loaded with diclofenac sodium that were produced utilizing the central composite design are shown.

Table 3: Central composite design for diclofenac sodium loaded solid lipid nanoparticles

Factor	Name	Units	Low Actual	High Actual	Low Coded	High Coded	Mean
A	Amount of stearic acid (gm)	molar	0.1	0.5	-1.000	1	0.3
B	Amount of Tween 80 (%w/v)	molar	0.2	1	-1.000	1	0.6
Y1	Percentage drug entrapment (%)						

Table 4: Central composite design batches and their obtained responses

Run	Factor 1 A:Amount of stearic acid (gm)	Factor 2 B:Amount of Tween 80 (%w/v)	Response 1 Percentage drug entrapment (%)
DDSLN1	0.582843	0.6	91.152
DDSLN2	0.1	0.2	64.265
DDSLN3	0.3	0.034315	81.966
DDSLN4	0.3	0.6	89.368
DDSLN5	0.3	1.165685	82.181
DDSLN6	0.017157	0.6	60.147
DDSLN7	0.3	0.6	84.554
DDSLN8	0.3	0.6	88.368

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DDSLN9	0.1	1	66.520
DDSLN10	0.3	0.6	88.956
DDSLN11	0.5	1	86.603
DDSLN12	0.5	0.2	88.368
DDSLN13	0.3	0.6	89.250

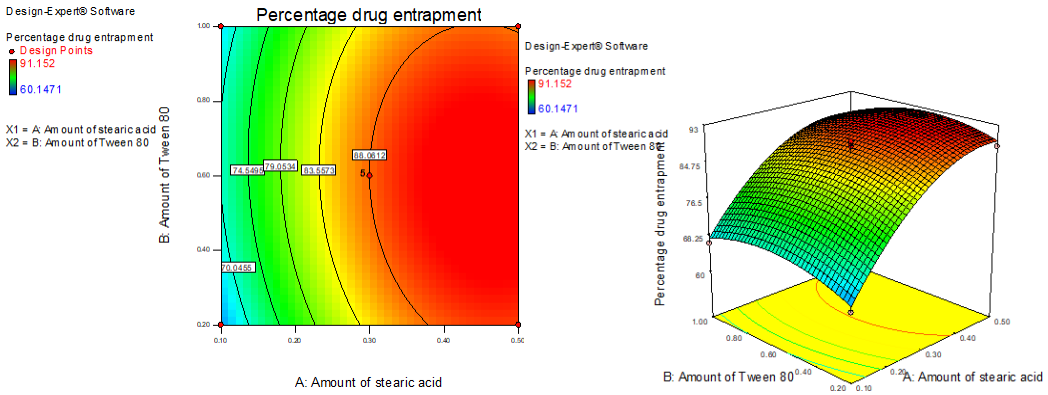

Figure 6: a) Counter plot and b 3D plot between Lipid (A), surfactant B) with % Entrapment (Y)

Table 5: Observed and Predicted value

Standard Order	Actual Value	Predicted Value	Residual	Leverage
1	64.265	65.542	-1.277	0.625
2	88.368	89.560	-1.192	0.625
3	66.520	67.750	-1.231	0.625
4	86.603	87.749	-1.146	0.625
5	60.147	58.876	1.271	0.625
6	91.152	90.000	1.152	0.625
7	81.966	80.722	1.244	0.625
8	82.181	81.003	1.179	0.625
9	88.368	88.099	0.269	0.2
10	88.956	88.099	0.857	0.2
11	84.554	88.099	-3.545	0.2
12	89.250	88.099	1.151	0.2
13	89.368	88.099	1.269	0.2

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3.6 In-Vitro Studies

The in vitro drug release of Diclofenac Sodium from the optimized SLN-loaded ceramide cream formulation was carried out using the dialysis bag method in phosphate buffer saline (PBS, pH 7.4) at 37 ± 0.5°C. The study showed a biphasic release pattern, characterized by an initial

Burst release attributed to surface- associated drug, followed by a sustained release phase extending up to 24 hours, indicating controlled diffusion of drug from the SLNs embedded in the cream base.

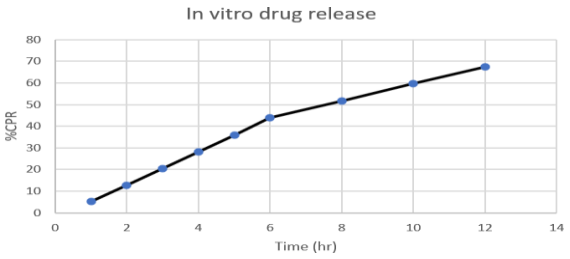

Fig 7 In vitro drug release

3.7 Physicochemical Evaluation of the Formulated Cream and *In-Vitro* Characterization of Diclofenac Sodium Loaded Solid Lipid Nanoparticles

3.7.1 Physical appearance

All formulations of diclofenac sodium- loaded solid lipid nanoparticles (DDSLN1–DDSLN13) were found to be uniform and homogeneous dispersions. No signs of phase separation, sedimentation, or aggregation were observed, indicating good Physical stability and consistency of the prepared batches. Visual observation indicated that prepared diclofenac sodium loaded solid lipid nanoparticles were uniform, homogenous in appearance.

3.7.2 Percentage drug entrapment

Percentage drug entrapment of all prepared diclofenac sodium loaded solid lipid nanoparticles formulations was found to be between 64.265±0.588% to 91.152±0.148%.

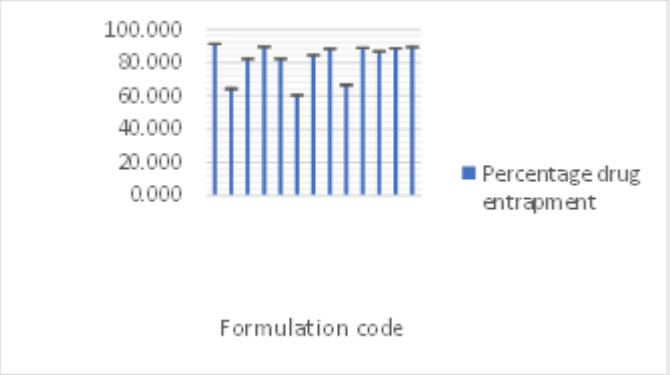

Figure 8 Percentage drug entrapment of the diclofenac sodium loaded solid lipid nanoparticles formulation

3.7.3 Vesicle size, PDI and zeta potential

Vesicle size and PDI of the optimized Formulation DDSLN14 were determined using the particle size analyzer.

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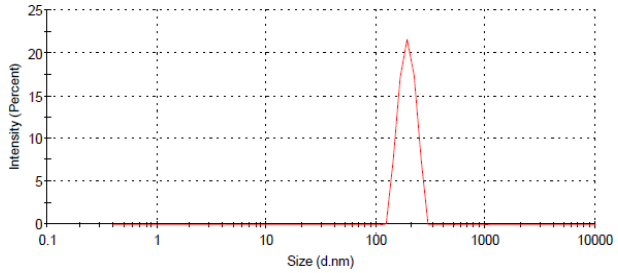

Figure 9: Vesicle size distribution of optimized formulation DDSLN14

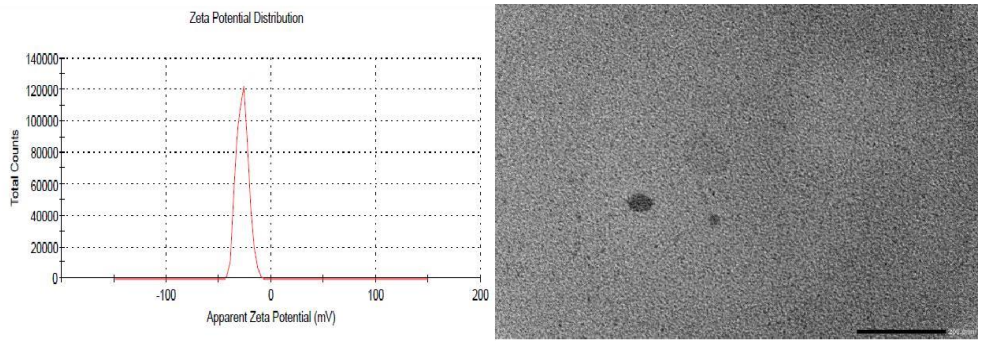

Figure 10: Zeta potential and TEM image of optimized formulation DDSLN14

The observation confirms that the vesicle size, PDI, and zeta potential of the formulation were found to be 224.9nm, 0.180, and -16.5mv respectively.

3.8 In-vitro characterization diclofenac sodium loaded solid lipid nanoparticle incorporated cream

A) Physical appearance

B) **pH and Spreadability**

All cream formulations containing diclofenac Sodium-loaded solid lipid nanoparticles (DDSLN14C1–DDSLN14C4) exhibited a uniform and homogeneous appearance, free from any signs of phase separation. This consistent observation indicates good physical stability and proper incorporation of nanoparticles within the cream base.

Table: 6 pH and Spreadability of the prepared formulations

S.No.	Formulation Code	pH (Mean ± SD)	Spreadability (gm·cm/sec) (Mean ± SD)
1	DDSLN14C1	5.977 ± 0.047	10.796 ± 0.273
2	DDSLN14C2	6.043 ± 0.025	5.302 ± 0.118
3	DDSLN14C3	6.093 ± 0.074	3.696 ± 0.096
4	DDSLN14C4	6.030 ± 0.046	2.825 ± 0.042

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Spreadability had a great significance in the application behavior and long-term stability of the skin cream in cosmetics as well as in pharmaceutical field. The spreadability of all formulations was shown in Table 7.15, with values ranging from 2.825±0.042 to 10.796±0.273gm.cm/sec. The spreadability property of the cream is influenced by the concentration of the lipid agent carbopol. Spreadability and lipid concentration are inversely with each other.

C) Viscosity and percentage Drug content

Viscosity is an important physical parameter that determines the extrudability, spreadability, and stability of semisolid preparations. Viscosity was measured using Brookfield viscometer.

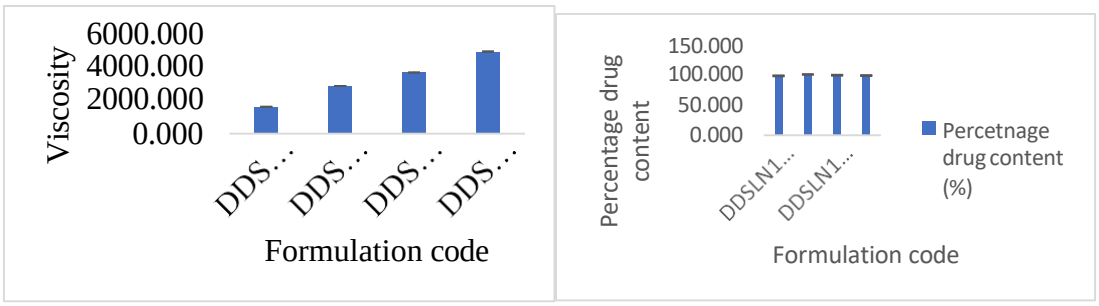

Figure 11: Viscosity and Percentage drug content of the all-prepared formulation

Among all four formulations, two formulations DDSLN14C2 and DDSLN14C3 formulation displayed the maximum drug content of the diclofenac sodium, which suggests uniform

D) **Percentage drug release**

Distribution of the drug in the solid lipid matrix. Based on the finding of the above characterization parameters the formulation DDSLN14C2 and DDSLN14C3 was selected for further evaluation.

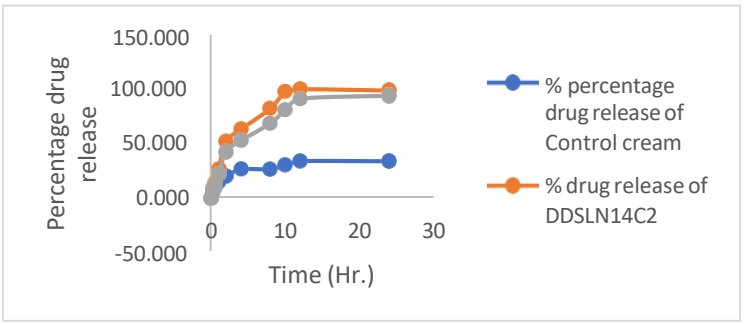

Figure 12: Percentage drug release of the DDSLN14C2 and DDSLN14C3, and control cream formulation

Due to the solid matrix of the nanoparticles and the subsequent drug different from that of diclofenac sodium. The PCS mean diameter of the SLN dispersion was 224.9 nm, whereas it was about 1 µm in the simple emulsion. The Percentage of released diclofenac sodium from control cream was lower than for SLN cream. The initial release within the first 6 hours was higher for the SLN cream formulation than for the control cream, which can be explained by

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low solubility and less permeation of drug from the simple cream. The prolonged Release in the from the SLN cream can be explained by slower diffusion of diclofenac sodium from the solid lipid of SLN. Formulation DDSLN14C3 have less release than the formulation DDSLN14C2. The reason could be the DDSLN14C3 possess higher viscosity due to higher amount of stearic acid in the cream. Formulation DDSLN14C2 release 98.676±1.013% of drug than the 93.971±0.882% from DDSLN14C3 and 33.132±0.318% from control cream.

E) Drug Release Kinetic Study

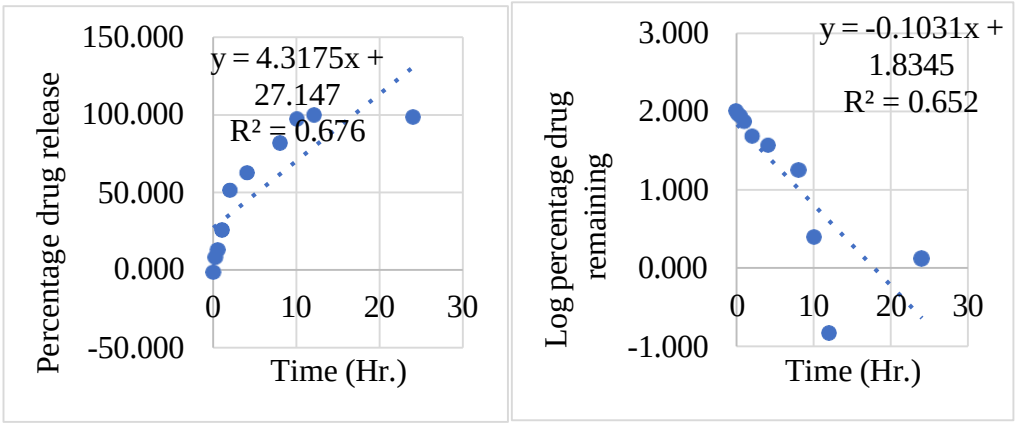

Figure 13: Zero and order kinetic mode for release of formulation from DDSLN14C2 respectively

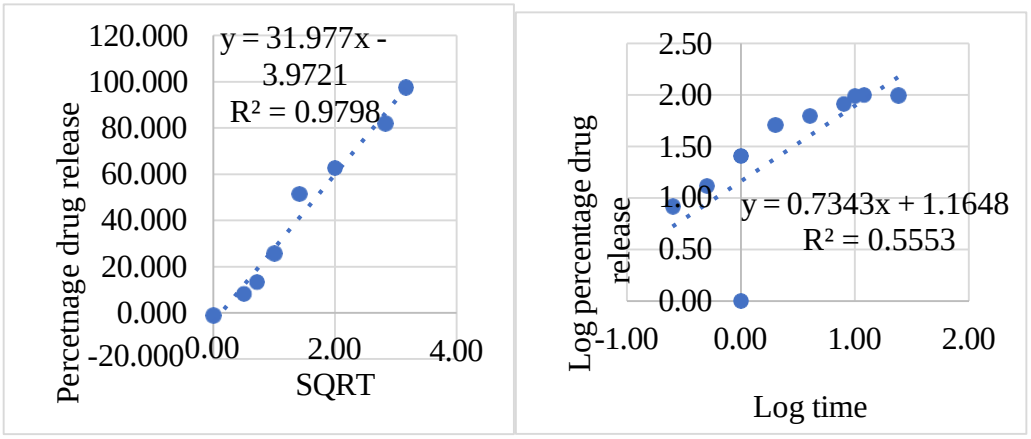

Figure 14: Higuchi and Korsmeyer peppas order kinetic mode for release from formulation DDSLN14C2 respectively

The correlation coefficients (R^2) values, showed that the release of diclofenac sodium from DDSLN14C2is best-fitted to Higuchi's model (diffusion mechanism), where it showed the highest (R^2) 0.9798.

Conclusion

The present study successfully formulated and

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optimized diclofenac sodium-loaded solid lipid nanoparticles (SLNs) and incorporated them into a cream base for topical delivery. Preformulation studies confirmed the physicochemical properties and identity of diclofenac sodium. Using a Central Composite Design, SLN Formulation DDSLN14 was optimized based on maximum drug entrapment efficiency (92.064 ± 0.044%)
using 0.47 g stearic acid and 0.46% Tween 80. The optimized nanoparticles showed favourable physicochemical characteristics, including vesicle size (224.9 nm), PDI (0.180), and zeta potential (-16.5 mV), along with spherical morphology confirmed via TEM. The SLN-incorporated cream formulations were evaluated for pH, spreadability, viscosity, drug content, and release behaviour. DDSLN14C2 and DDSLN14C3 demonstrated optimal performance, with drug content above 98% and release extending up to 24 hours. DDSLN14C2 showed the highest release (98.676 ± 1.013%), attributed to lower viscosity compared to DDSLN14C3. The release kinetics followed the Higuchi model (R^2
= 0.9798), indicating diffusion- controlled drug release.

In conclusion, SLNs significantly enhanced the controlled release and skin compatibility of diclofenac sodium. These findings suggest that SLN-based cream formulations can be a promising alternative to conventional topical preparations for effective and sustained anti-inflammatory therapy.

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